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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
02/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/593,071	ROUGEOT ET AL.	
	Examiner	Art Unit	
	DONG JIANG	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-20,22-64,66 and 67* is/are pending in the application.

4a) Of the above claim(s) *10-14,17-19,22-64 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,15,16,20 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3-20,22-64,66 and 67* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 05 November 2009 is acknowledged and entered. Following the amendment, claims 2, 21 and 65 are canceled, claims 1, 4-9, 15, 16, 22, 25, 27 and 30 are amended, and the new claim 67 is added.

Currently, claims 1, 3-20, 22-64, 66 and 67 are pending, and claims 1, 3-9, 15, 16, 20 and 67 are under consideration. Claims 10-14, 17-19, 22-64 and 66 remain withdrawn from further consideration as being drawn to a non-elected invention.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 2, 21 and 65 are moot as the applicant has canceled the claims.

Formal Matters:

Claims

Claim 1 is objected to for the following informalities, and appropriate correction is required for each item:

The claim recites "the Basic Proline-rich Lacrimal Protein" in lines 1-2. "The *human* Basic Proline-rich Lacrimal Protein" is suggested if SEQ ID NO:2 is intended (as indicated in applicants response, page 23).

Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-9, 15, 16 and 20 remain rejected, and claim 67 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of

record set forth in the last Office Action mailed on 8/5/09, at pages 3-4, and for the reasons below.

Applicants argument filed on 05 November 2009 has been fully considered, but is not deemed persuasive for the reasons below.

At page 21 of the response, the applicant argues that the rejection is believed to be obviated by amendment. This argument is not persuasive for the following reasons: the newly amended claim 1 remains indefinite for the recitation "wherein said peptide ... is obtained by cleavage of the BPLP protein precursor by furin, a PC convertase, or PACE 4" because it is unclear as to what it is meant as both furin and PACE4 are PC convertases.

The newly amended claims 15 and 16 recite "a mimetic thereof, ..., wherein said mimetic ... is obtained through a structural modification selected from the group consisting of ...". However, it is unclear based on what the structural modification is added/made. Further, according to the "definition" in the specification: a "mimetic" is a molecule that *mimics some properties* of the natural peptides, preferably their binding specificity and physiological activity (page 10, lines 6-8). There is no mention about the basic structure of the "mimetic" in the definition, thus, it reads on any or all functional equivalents without structural limitation. Only in the preferred embodiment, it indicates that "preferred mimetics are obtained by structural modification *of peptides* according to the invention, ..." (page 10, lines 8-9). Thus, the provided definition is not considered, in itself, to provide definitive structural limitation for the claimed mimetic. As the claims do not specify that said mimetic is obtained by structural modification of said peptide, the metes and bounds of the claims, therefore, cannot be determined.

The remaining claims are included in this rejection because they are dependent from the specifically mentioned claims without resolving the indefiniteness issue belonging thereto.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 5, 7-9 and 67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Claims 5 and 7-9 are directed to a peptide *consists of* any one of SEQ ID NO:3-6; and claim 67 is directed to the peptide *consisting of* 3 to 15 amino acids. As these claims are dependent from claim 1, said peptide would be necessarily "obtained by cleavage of the BPLP protein precursor by furin, a PC convertase, or PACE 4" (claim 67 also repeats this limitation). The specification demonstrates the naturally occurring 5 amino acids peptide fragment (with a sequence QRFSR) in human saliva by amino acid sequence analysis of the low molecular weight form isolated from saliva (eluted from the ultimate RP-HPLC at 18 min-retention time (fraction 20) corresponded to 690 and 769.5 Da molecular mass) (page 43-45, Example 3). However, it is unlikely that such a fragment could be obtained by cleavage of the BPLP by a PC convertase alone such as furin or PACE 4 (as claimed) because neither the prior art has established, nor the instant specification has demonstrated that the claimed peptides can be obtained by cleavage of the BPLP protein precursor (SEQ ID NO:2) by said enzymes, and because the art indicates otherwise. For instance, Duckert et al. (*Protein Engineering, Design and Selection*, 2004, 17(1): 107-112) teaches that seven mammalian kexin-related proprotein convertases have been identified: PC1, PC2, furin, PC4, PC5, PACE4 and PC7 (page 107, 2nd column, 2nd paragraph); that the PC enzymes process precursors at sites, which usually contain the consensus sequence [R/K]–X_n–[R/K]↓, where X indicates any amino acid residue, *n*, the number of spacer amino acid residues, is 0, 2, 4 or 6; that furin has a more stringent substrate specificity and preferentially recognizes sites that contain the sequence motif R–X–[R/K]–R↓ (page 107, 2nd column, 3rd paragraph). In the instant case, the polypeptide of SEQ ID NO:2 does not have two of such a site (according to Duckert), which are near to each other to allow the generation of said peptide fragment such as QRFSR of SEQ ID NO:3. Further the specification provide no guidance and/or working example demonstrating the claimed peptide fragments could be obtained by said enzymatic cleavage. Therefore, the method step of the enzymatic cleavage would not enable one skilled in the art to obtain the peptide fragments as claimed. While the claimed peptide fragments can be obtained by peptide synthesis, or by isolation from its natural source, it would

not be obtainable by said method step in the claim (claim 1). Elimination of the method step ("is obtained by cleavage of the BPLP protein precursor by furin, a PC convertase, or PACE 4") would be remedial.

Written Description

Claims 1, 3, 15, 16 and 20 remain rejected, and the new claim 67 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly amended independent claim 1 recites "wherein said peptide comprises *3 to 15* amino acids and is obtained by cleavage of the BPLP protein precursor by furin, a PC convertase, or PACE 4", and said peptide derivative is obtained from said peptide by *one to two* amino acid substitutions and said peptide derivative retains the binding specificity and/or physiological activity of said peptide", Which encompass 1) all enzyme-digested peptide fragments from the entire BPLP polypeptide, which meet the structural (comprises 3 to 15 amino acids) and functional limitations; 2) the fragments that are 3 amino acids long, and retain the functional property; and 3) the fragments that are 3 amino acids long with one to two amino acids substitutions, and still retain the functional property.

The specification merely teaches *one* core sequence for the claimed peptides, derived from one region of the human BPLP polypeptide of SEQ ID NO:2, wherein the core sequence has 5 amino acids: QRFSR (SEQ ID NO:3, for example), which corresponds to amino acids 22-26 of the human BPLP of SEQ ID NO:2. All other fragments claimed or taught in the specification comprise the core sequence "RFSR", and were derived by adding or substituting one amino acids at the N-terminus of the core sequence (SEQ ID NO:4-7, for example). No functional fragment derived from other regions of the BPLP polypeptide; functional fragment of 3 amino acids; or functional fragment of 3 amino acids with one to two amino acids substitutions, meeting the limitation of the claim was ever identified or particularly described.

Further, as addressed in the last Office Action, the specification teaches five peptide derivatives of SEQ ID NO:3, and they are SEQ ID NO:4, 5, 7, and the last two in the Table on page 46. However, *only* peptide of SEQ ID NO:4 showed comparable potency towards a human

and rat ectoendopeptideases as that of peptide of SEQ ID NO:3 (page 46, Table, and lines 8-14), and SEQ ID NO:5 and 7 do not seem ever being tested. Thus, only *one* molecule from each claimed genus (a peptide of maturation product of a BPLP (SEQ ID NO:3), and a peptide derivative thereof (SEQ ID NO:4)) meeting the limitation of the claims was ever identified. With respect to claim 20, the specification merely disclosed *one* BPLP, the human BPLP of SEQ ID NO:2, and no other BPLP meeting the limitation of the claim were ever identified or particularly described. Accordingly, the specification does not provide adequate written description of the claimed genus.

Applicants argument filed on 05 November 2009 has been fully considered, but is not deemed persuasive for the reasons below.

At pages 22-23 of the response, the applicant argues that the claims have been amended to structurally define the claimed peptides and the peptide derivatives (specify the minimal length of the peptide as 3-15 amino acids, and to specify that the peptide derivative does not comprise more than two substitutions compared to the peptide and that it retains binding specificity and/or physiological activity of the peptide. Applicants further argue that the skilled artisan would readily obtain the claimed peptides by the enzymatic cleavage of the BPLP protein; readily envision and be able to produce the peptide derivatives by introducing one or two substitutions into the sequence of the peptide thus obtained; and readily envision and be able to produce mimetics by introducing one of the structural modifications recited in the claims; and that verification of the resultant peptides, peptide derivatives, and mimetics that inhibit metalloectopeptidases can be readily attained by employing the assay described in Example 4 of the specification. This argument is not persuasive because the issue is *not* whether the skilled artisan would be able to obtain the peptide by enzyme digestion, to make amino acid substitutions or the structural modifications, or to perform the functional assay, rather, the issue is that the specification does not provide adequate written description for the claimed genus of the peptides, or derivatives and mimetics thereof (only *one* species of the peptide represented by QRFSR was described). The first paragraph of 35 U.S.C. § 112 "requires a 'written description of the invention' which is separate and distinct from the enablement requirement." "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. Adequate written description requires more than a

mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483.

At page 23 of the response, the applicant argues, with respect to claim 20, that the specification clearly defines the term "BPLP protein" as being a 201 amino acid-long sequence of SEQ ID NO: 2 (see page 5, lines 27-32), and that the designation of BPLP is known in the art (see, for example, Dickinson et al), thus, Applicants submit that the skilled artisan would immediately understand that the term BPLP protein refers to the protein of SEQ ID NO: 2. This argument is not persuasive because the specification merely states "the human gene BPLP codes for a polypeptide sequence of 201 amino-acids ... (Dickinson and Thiesse, 1996). The gene BPLP is expressed in human lacrimal and submandibular glands. In the annexed sequence listing, SEQ ID NO:1 shows the cDNA sequence coding for BPLP, and SEQ ID NO:2 shows the BPLP amino acid sequence." While such statement defines the sequence structure of the human BPLP, there is no indication in the claims (claims 1 and 20, for example), *as written* ("the BPLP", or "a BPLP"), that they only encompass the human BPLP.

Therefore, as indicated previously, in the instant case, only the peptides of SEQ ID NO:3-6, and the human BPLP of SEQ ID NO:2, but not the full breadth of the claims ("peptide derivative", "mimetic of a peptide", "a BPLP protein", and "3 to 15 amino acids and is obtained by cleavage of the BPLP protein precursor by furin, a PC convertase, or PACE 4") meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 6, 15, 16 and 20 remain rejected under 35 U.S.C. 102(b) as being anticipated by Dickinson et al. (Curr Eye Res. 1996 Apr;15(4):377-86, provided by applicants), for the reasons of record set forth in the last Office Action mailed on 8/5/09, at page 8, and for the reasons below.

Applicants argument filed on 05 November 2009 has been fully considered, but is not deemed persuasive for the reasons below.

At pages 23-24 of the response, the applicant argues that claim 1 has been amended to specify that the peptide is obtained by cleavage of the BPLP protein precursor by furin, a PC convertase, or PACE 4, that the mature form of BPLP, obtained through cleavage of the signal peptide by a signal peptidase, is therefore excluded from the scope of the peptides of the present invention, as such, Dickinson does not affect the patentability of the claimed invention. This argument is not persuasive for the following reasons: the presently claimed peptides are a part of the BPLP of SEQ ID NO:2 taught by Dickinson. QRFSR of SEQ ID NO:3, for example, correspond to amino acids 1-5 of Dickinson's mature form of BPLP of SEQ ID NO:2, indicating the same enzyme cleavage at the N-terminus of both Dickinson's mature form of BPLP and the present peptide, in the absence to the contrary. Therefore, Dickinson's mature form of BPLP of SEQ ID NO:2 would meet the structural limitation of the peptide in the claims: "*comprises* 3 to 15 amino acids and is obtained by cleavage of the BPLP protein precursor by furin, a PC convertase, or PACE; and the reference anticipates the claims.

Conclusion:

No claim is allowed.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Examiner Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Dong Jiang/
Primary Examiner, Art Unit 1646
1/28/10